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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/251,274	02/16/99	DI RIENZO A	27373/35172

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ART UNIT	**PAPER NUMBER**
1655	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/251,274	Di Rienzo et al.
Examiner	**Group Art Unit**
Arun Chakrabarti	1655

☒ *Responsive to communication(s) filed on* Oct 16, 2000 .

☒ *This action is* **FINAL.**

☐ *Since this application is in condition for allowance except for formal matters,* **prosecution as to the merits is closed** *in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.*

A shortened statutory period for response to this action is set to expire 3 *month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).*

Disposition of Claims

☒ *Claim(s)* 1-62 and 70-75 *is/are pending in the application.*

Of the above, claim(s) _____ *is/are withdrawn from consideration.*

☐ *Claim(s)* _____ *is/are allowed.*

☒ *Claim(s)* 1-62 and 70-75 *is/are rejected.*

☐ *Claim(s)* _____ *is/are objected to.*

☐ *Claims* _____ *are subject to restriction or election requirement.*

Application Papers

☐ *See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.*

☐ *The drawing(s) filed on* _____ *is/are objected to by the Examiner.*

☐ *The proposed drawing correction, filed on* _____ *is* ☐*approved* ☐*disapproved.*

☐ *The specification is objected to by the Examiner.*

☐ *The oath or declaration is objected to by the Examiner.*

Priority under 35 U.S.C. § 119

☐ *Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).*

☐ *All* ☐ *Some** ☐ *None of the CERTIFIED copies of the priority documents have been*

☐ *received.*

☐ *received in Application No. (Series Code/Serial Number)* _____ .

☐ *received in this national stage application from the International Bureau (PCT Rule 17.2(a)).*

**Certified copies not received:* _____ .

☐ *Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).*

Attachment(s)

☒ *Notice of References Cited, PTO-892*

☒ *Information Disclosure Statement(s), PTO-1449, Paper No(s).* 10

☐ *Interview Summary, PTO-413*

☐ *Notice of Draftsperson's Patent Drawing Review, PTO-948*

☐ *Notice of Informal Patent Application, PTO-152*

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Specification

1. Applicant's declaration under Rule 131 is not sufficient to overcome the 102 (a) rejection as anticipated by Beutler et al. (Proceedings of the National Academy of Sciences, USA) (July, 1998) (Vol.95, pages 8170-8174) because of the following reason. "The 37 CFR 1.131 affidavit or declaration must establish possession of either the whole invention claimed or something falling within the claim (such as species of a claimed genus), in the sense that the claim as a whole reads on it. In re Tanczyn, 347 F.2d 830, 146 USPQ 298 (CCPA 1965)", See MPEP 715.01 ©. The 37 CFR 1.131 affidavit or declaration provided by the applicant on October 16, 2000, contains an abstract presented at ninety-ninth annual meeting of American Society for Clinical Pharmacology and Therapeutics (March 30-April 1, 1998) held at New Orleans, Louisiana, USA. This abstract teaches that the presence of five TA repeats in UGT gene promoter correlates with increased expression of the gene (lines 22-23) but this abstract does not teach that presence of eight repeats correlates with decreased expression of the gene which is an important and essential part of all the base claims. The correlation of increased expression of the gene is not a species of a claimed genus of correlation of decreased expression. Therefore, the 37 CFR 1.131 affidavit or declaration presented by the applicant clearly failed to establish possession of either the whole invention claimed or something falling within the claim (such as

species of a claimed genus), in the sense that the claim as a whole reads on it. Accordingly, the 102 (a) and 103 (a) rejections based on the Beutler reference are hereby maintained.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-30 and 70-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 9, 16 and 24 are rejected over the recitation of the word "or". Regarding claims 1, 9, 16 and 24 , the word "or" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 75 is rejected over the recitation of the phrase "The method of claim 31 or 31". It is not clear why the same limitations of claim 31 have been inserted twice in the same claim. The metes and bounds of the claim is vague and indefinite. Necessary correction is required.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 1-30 and 70-73 are rejected under 35 U.S.C. 102 (a) as anticipated by Beutler et al. (Proceedings of the National Academy of Sciences, USA) (July, 1998) (Vol.95, pages 8170-8174).

Beutler et al teaches a method for detecting polymorphisms in a uridine diphosphate glucuronosyltransferase (UGT1A1) gene promoter (Abstract) comprising determining the presence of five or eight thymidine-adenine (TA) repeats in the promoter (MATERIALS AND METHODS SECTION and Figure 1), wherein the presence of five TA repeats correlates with increased expression of the gene and the presence of eight repeats correlates with decreased expression of the gene (Abstract, Page 8170, column 1, line 29 to column 2, line 18, and DISCUSSION Section, first four paragraphs, Figures 2A-2D, Page 8173, second paragraph).

Beutler et al teaches a method comprising the steps of:

a) obtaining DNA from an individual (MATERIALS AND METHODS SECTION , lines 1-9).

b) amplifying all or part of the UGT gene promoter contained in the DNA by PCR (MATERIALS AND METHODS SECTION , Determination of UGT1A1 Promoter genotypes Subsection, lines 3-12).

c) determining the number of TA repeats in the promoter by sequencing gel electrophoresis of the amplified DNA (MATERIALS AND METHODS SECTION , Determination of UGT1A1 Promoter genotypes Subsection, lines 12-25 and Figure 1).

Beutler et al teaches a method wherein the polymorphism comprises an allele, the allele selected from the group consisting of five TA repeats, [TA]5, six TA repeats, [TA]6, seven TA repeats, [TA]7, and eight TA repeats, [TA]8 (MATERIALS AND METHODS SECTION , Determination of UGT1A1 Promoter genotypes Subsection, lines 22-25 and Figure 1).

Beutler et al teaches a method wherein the promoter has a genotype selected from the group consisting of [TA]6/[TA]8, [TA]7/[TA]8, and [TA]8/[TA]8.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-62 and 70-73 are rejected under 35 U.S.C. 103 (a) over Beutler et al. (Proceedings of the National Academy of Sciences, USA) (July, 1998) (Vol.95, pages 8170-8174) in view of Clarke et al. (Handbook of Experimental Pharmacology, (1994), Vol. 112, pages 3-43).

Beutler et al teach the method of claims 1-30 and 70-73 as described above.

Beutler et al does not teach the method of screening individuals for variation in activity of glucuronidation of drugs and xenobiotics and a method for optimizing drug dosage and a method for predicting an individual's sensitivity to xenobiotics.

Clarke et al teach the method of screening individuals for variation in activity of glucuronidation of drugs and xenobiotics by UDPGT and a method for optimizing drug dosage and a method for predicting an individual's sensitivity to xenobiotics (Page 20, Human Uridine Diphosphate Glucuronosyltransferase Isoforms Subsection, SECTION E, page 24 to page 28, Tables 1-4).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the classical glucuronidation of drugs and xenobiotics by UDPGT model of Clarke et al. in the method of Beutler et al., since Clarke et al. states "Such method should prove to be of great benefit to the pharmaceutical industry as drugs which have cytotoxic glucuronides or are metabolized too rapidly to be of therapeutic value can be identified, chemically modified and improved (Page 28, last 4 lines)." Clarke et al expressly connect Gilbert syndrome and dosage effects of Acetaminophen to UGT gene, while Beutler et al connect UGT mutation to Gilbert syndrome and to promoter activity, thereby connecting the Acetaminophen dosage and metabolism to the activity of the UGT gene promoter. An ordinary practitioner would have been motivated to combine and compare the classical glucuronidation of drugs and xenobiotics by UDPGT model of Clarke et al. in the method of Beutler et al in order to achieve the express advantages noted by Clarke et al. of the glucuronidation techniques which

can provide method of great benefit to the pharmaceutical industry as drugs which have cytotoxic glucuronides or are metabolized too rapidly to be of therapeutic value can be identified, chemically modified and improved.

8. Claims 1-62 and 70-75 are rejected under 35 U.S.C. 103 (a) over Beutler et al. (Proceedings of the National Academy of Sciences, USA) (July, 1998) (Vol.95, pages 8170-8174) in view of Clarke et al. (Handbook of Experimental Pharmacology, (1994), Vol. 112, pages 3-43) further in view of Hausheer et al. (U.S. Patent 6,066,645).

Beutler et al. in view of Clarke et al teach method of claims 1-62 and 70-73 as described above.

Beutler et al. in view of Clarke et al do not teach the method wherein the drugs are Irinotecan and TAS-103.

Hausheer et al teach the method wherein the drugs are Irinotecan and TAS (Column 3, lines 20-22).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the commonly known commercially approved antineoplastic agents of Hausheer et al. in the method of Beutler et al., since Hausheer et al. states "The objective of all antineoplastic drugs is to eliminate (cure) or to retard the growth and spread (remission) of the cancer cells. The majority of the above listed agents pursue this objective by possessing primary cytotoxic activity, effecting a direct kill on the cancer cells (Column 3, line 66 to column 4, line 4)." An ordinary practitioner would have been motivated to

combine and compare the commonly known commercially approved antineoplastic agents of Hausheer et al. in the method of Beutler et al in order to achieve the express advantages noted by Hausheer et al. of the antineoplastic agents possessing primary cytotoxic activity, effecting a direct kill on the cancer cells.

Response to Amendment

9. In view of the amendment, 102 (b) rejection based on Bosma et al reference has been withdrawn.

Response to Arguments

10. Applicant's arguments filed on have been fully considered but they are not persuasive.

A) Applicant argued to withdraw Buetler et al reference in view of the submission of declaration under Rule 131 by the applicant. This argument is not persuasive as clearly explained in the Specification Section.

B) In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

It has been clearly mentioned in the 103 rejection, "Clarke et al expressly connect Gilbert syndrome and dosage effects of Acetaminophen to UGT gene, while Beutler et al connect UGT mutation to Gilbert syndrome and to promoter activity, thereby connecting the Acetaminophen dosage and metabolism to the activity of the UGT gene promoter (First Office Action) ".

Applicant argues that Clarke reference does not teach a method for optimizing drug dosage or predicting an individual's sensitivity to drugs. This argument is not persuasive. In Table 1 of Clarke reference, a list of several xenobiotics with cross references on column 3 of the same table is provided which clearly and obviously teach a method for optimizing drug dosage or predicting an individual's sensitivity to drugs.

Applicant argues that Clarke reference teaches away from the method for optimizing drug dosage or predicting an individual's sensitivity to drugs. Applicant argues that because Clarke has a preferred embodiment of review of glucuronidation by different drugs, Clarke reference is limited to the preferred embodiment. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states, " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Clarke has a preferred embodiment, this embodiment does not prevent the reference from suggesting broader embodiments in the disclosure and that this does not constitute a teaching away. For example, see page 26, lines 26-29.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph. D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600
1/2/01

Arun Chakrabarti,

Patent Examiner,

December 23, 2000